

HIGH PRESSURE COMPACTION FOR PHARMACEUTICAL FORMULATIONS

5 BACKGROUND OF THE INVENTION

Field of the Invention.

The invention relates to the field of pharmacology and, in particular, to sustained-release formulations for active pharmaceutical ingredients. The invention also relates to methods for preparing such formulations by high pressure compaction
10 of an active pharmaceutical ingredient.

Description of the Related Art.

Many pharmaceutical preparations are formulated as solid particles for oral ingestion or parenteral injection. Therefore, it is necessary that the active
15 pharmaceutical ingredient eventually dissolve into the surrounding fluids in order to be absorbed into the body. However, many drugs have low solubility in water. See, e.g., Remington: The Science and Practice of Pharmacy, 20th Ed. (2000), Lippincott Williams & Wilkins, Baltimore, pg. 209, Table 16-1. Therefore, formulations of very small particles have generally been preferred in the art because of their greater ease of
20 suspension and because a greater surface area to volume ratio typically results in more rapid dissolution. Thus, low solubility active pharmaceutical ingredients frequently have been formulated as micronized preparations in which the particles are typically < 10 μm in diameter. Such microparticles have been used to prepare solutions or suspensions for oral, subcutaneous, intravenous, intramuscular or other injectable
25 routes of administration; have been mixed with binding agents and pressed into pills or tablets for oral or rectal administration; and have been mixed with matrix materials to create implants in which the active pharmaceutical ingredient dissolves from the implant over time.

In certain situations, however, it is desired that an active pharmaceutical
30 ingredient is administered in a sustained-release formulation, typically with the objective of achieving nearly constant or zero-order kinetics of release over a sustained period of time.

Most sustained-release systems in the prior art have employed a finely milled or micronized preparation of the active pharmaceutical ingredient as a starting point in
35 the formulations. The release of the active pharmaceutical ingredient into the body is

then controlled using matrices, membranes or other inactive ingredients or devices. Examples of methods and devices known in the art for sustained release formulations include liposomes, bioerodible matrices (e.g., PLA/PGLA matrices), drug-permeable implants (e.g., U.S. Pat. No. 3,993,073 to Zaffaroni), implants with drug-permeable
5 and drug-impermeable membranes (e.g., U.S. Pat. No. 5,378,475 to Smith et al.), and osmotic drug delivery systems (e.g., U.S. Pat. No. 4,439,196 to Higuchi).

Pharmaceuticals particles can be produced by constructive or destructive means. Constructive means include crystallization, spray drying, freeze drying, and supercritical fluid techniques. Destructive techniques include machining or milling
10 using compressive forces, shear and tension forces. See, e.g., Crowder et al., A Guide to Pharmaceutical Particulate Science, (2003), CRC Press, pgs. 9-26.

In prior art sustained-release formulations, active pharmaceutical ingredients are usually machined or milled to produce small or micronized crystals of the drug, which are then combined with matrices, semi-permeable membranes, pumps or other
15 inactive ingredients or devices in order to achieve the effect of sustained-release delivery.

Prior art sustained-release delivery systems with large particles of an active pharmaceutical ingredient, such as insulin, corticosteroids, or penicillins, employ techniques as solvation crystallization, thermal crystallization, or seeding
20 crystallization to produce the larger particles.

SUMMARY OF THE INVENTION

The present invention depends, in part, upon the discovery that the application of high pressure compaction to powdered or micronized pharmaceutical preparations
25 can cause physical but non-chemical transformations to an alternative state with substantially slower rates of dissolution and, consequently, increased utility in the preparation of sustained-release formulations. In particular, pharmaceutical preparations subjected to high pressure compaction exhibit dissolution kinetics which are superior to conventional crystalline or amorphous packed powder preparations for
30 sustained-release administration of active pharmaceutical ingredients.

Thus, in one aspect, the present invention provides methods for producing a pharmaceutical preparation of pressure-fused particles including an active pharmaceutical ingredient by providing a sample including the active pharmaceutical ingredient in crystalline or amorphous form; subjecting the sample to high pressure
5 compaction at a pressure of between 0.1 GPa and 10 GPa to produce a compacted sample; and isolating pressure-fused particles from the compacted sample.

In some embodiments, the pressure is between 0.5 GPa and 7.5 GPa. In other embodiments, the pressure is between 1 GPa and 5 GPa.

In some embodiments, the amount of pressure is sufficient to produce a
10 compacted sample having a density of between 1 g/cm³ and 40 g/cm³, between 2 g/cm³ and 20 g/cm³, and between 4 g/cm³ and 10 g/cm³. In some embodiments, the amount of pressure is sufficient to produce pressure-fused microparticles having a density of between 1 g/cm³ and 40 g/cm³, between 2 g/cm³ and 20 g/cm³, and between 4 g/cm³ and 10 g/cm³.

15 In some embodiments, the compacted sample has a thickness of between 25 μm and 400 μm. In other embodiments, the compacted sample has a thickness of between 50 μm and 200 μm. In yet other embodiments, the compacted sample has a thickness of between 100 μm and 150 μm.

In some embodiments, the pressure is maintained for a period of between 30
20 sec. and 10 min. In other embodiments, the pressure is maintained for a period of between 60 sec. and 5 min. In yet other embodiments, the pressure is maintained for a period of between 90 sec. and 3 min.

In some embodiments, the pressure-fused particles have a maximum dimension between 20 μm and 800 μm. In other embodiments, the pressure-fused
25 particles have a maximum dimension between 40 μm and 400 μm. In yet other embodiments, the pressure-fused particles have a maximum dimension between 100 μm and 250 μm.

In some embodiments, the step of isolating the pressure-fused particles from the compacted sample comprises sieving the compacted sample through a sieve with
30 an exclusion limit of between 20 μm and 800 μm. In other embodiments, the

exclusion limit is between 40 μm and 400 μm . In yet other embodiments, the exclusion limit is between 100 μm and 250 μm .

In some embodiments, the sample prior to compaction includes micronized particles including the active pharmaceutical ingredient.

5 In another aspect, the invention provides pharmaceutical preparations of pressure-fused particles comprising an active pharmaceutical ingredient in which the pressure-fused particles include an active pharmaceutical ingredient subjected to high pressure compaction at a pressure of between 0.1 GPa and 10 GPa. In some embodiments, the pressure is between 0.5 GPa and 7.5 GPa. In other embodiments,
10 the pressure is between 1 GPa and 5 GPa.

In some embodiments, the pressure-fused particles have a maximum dimension between 20 μm and 800 μm . In other embodiments, the pressure-fused particles have a maximum dimension between 40 μm and 400 μm . In yet other embodiments, the pressure-fused particles have a maximum dimension between 100
15 μm and 250 μm .

These and other embodiments and advantages of the present invention will be apparent to one of skill in the art from the following detailed description of the invention and certain embodiments and examples.

20 BRIEF DESCRIPTION OF THE DRAWINGS

The following drawing is illustrative of embodiments of the invention and is not meant to limit the scope of the invention as encompassed by the claims.

Figure 1 presents data regarding the *in vitro* release of the active pharmaceutical ingredient olanzapine from coated microparticles of the invention over
25 a sustained-release period.

Figure 2 presents data regarding the *in vivo* release of the active pharmaceutical nifedipine from a compacted sample including pressure-fused microparticles of the invention over a sustained-release period.

Figure 3 presents data regarding the *in vivo* release of the active
30 pharmaceutical carbamazepine from a compacted sample including pressure-fused microparticles of the invention over a sustained-release period.

Figure 4 presents data regarding the *in vivo* release of the active pharmaceutical cyclosporine from a compacted sample including pressure-fused microparticles of the invention over a sustained-release period.

Figure 5 presents data regarding the *in vivo* release of the active pharmaceutical ciprofloxacin from a compacted sample including pressure-fused microparticles of the invention over a sustained-release period.

DETAILED DESCRIPTION

The patent, scientific and medical publications referred to herein establish knowledge that was available to those of ordinary skill in the art at the time the invention was made. The entire disclosures of the issued U.S. patents, published and pending patent applications, and other references cited herein are hereby incorporated by reference.

15 Definitions.

All technical and scientific terms used herein, unless otherwise defined below, are intended to have the same meaning as commonly understood by one of ordinary skill in the art. References to techniques employed herein are intended to refer to the techniques as commonly understood in the art, including variations on those techniques or substitutions of equivalent or later-developed techniques which would be apparent to one of skill in the art. In addition, in order to more clearly and concisely describe the subject matter which is the invention, the following definitions are provided for certain terms which are used in the specification and appended claims.

25 Particle. As used herein, the term "particle" means any solid preparation of a compound. Although the particles of the invention are substantially spherical in some embodiments, the particles can be any solid geometric shape which is not inconsistent with the principles of the invention, including, without limitation, ellipsoids, cylinders, polyhedrons, disks and irregular shapes.

30 Disk. As used herein, the term "disk" means any solid body which is significantly smaller in a first dimension relative to the two perpendicular dimensions.

Such bodies may be variously described as disks, wafers, or planar bodies, including, without limitation, bodies which are circular, elliptical or polygonal in the plane perpendicular to the first dimension.

5 Active Pharmaceutical Ingredient. As used herein, the term "active pharmaceutical ingredient" means any compound which has utility as a pharmaceutical or drug, including, without limitation, naturally occurring compounds (e.g., hormones) and synthetic drugs.

Sustained Release. As used herein, the term "sustained-release" means continued release of a compound from a reservoir or source over a period of time.

10 Parenteral Administration. As used herein, the term "parenteral administration" means introduction of a pharmaceutical preparation into the body by a route other than the alimentary canal or digestive tract, including, without limitation, subcutaneous, intravenous, intramuscular and intraocular injection as well as surgical implantation.

15 Polymeric Coating. As used herein, the term "polymeric coating" means any coating which is formed by polymerization of one or more monomers to form linear or branched or cross-linked macromolecules. The coating may be variously characterized as a coating, layer, membrane, shell, capsule, or the like, and must substantially surround or envelope the core particles of the invention.

20 Permeable. As used herein, the term "permeable" means allowing passage of molecules by diffusion but not by fluid flow.

Semi-Permeable. As used herein, the term "semi-permeable" means permeable to some molecules but not to others. As used herein, semi-permeable polymeric coatings are permeable to at least water and the active pharmaceutical
25 ingredient within the particles of the invention.

Biocompatible. As used herein, the term "biocompatible" means characterized by not causing a toxic, injurious or immunological response when brought into contact with living tissue, particularly human or other mammalian tissue.

Biodegradable. As used herein, the term "biodegradable" means capable of
30 partially or completely dissolving or decomposing in living tissue, particularly human

or other mammalian tissue. Biodegradable compounds can be degraded by any mechanism, including, without limitation, hydrolysis, catalysis and enzymatic action.

Pseudo-Zero-Order Kinetics. As used herein, the term "pseudo-zero-order kinetics" means sustained-release of the active pharmaceutical ingredient which exhibits kinetics which is zero-order (i.e., independent of concentration) or between zero-order and first order (i.e., proportional to concentration) kinetics over the sustained-release period, where the concentration is based on the total amount of the active pharmaceutical ingredient contained within the particles. In some embodiments, the release exhibits kinetics which are less than proportional to the square root of the concentration of the active pharmaceutical ingredient over the sustained-release period.

Or. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

Numerical Ranges. As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value within the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value within the numerical range, including the end-points of the range. As an example, and without limitation, a variable which is described as having values between 0 and 2 can take the values 0, 1 or 2 if the variable is inherently discrete, and can take the values 0.0, 0.1, 0.01, 0.001, or any other real values ≥ 0 and ≤ 2 if the variable is inherently continuous.

25 Pharmaceutical Formulation by High Pressure Compaction.

The present invention depends, in part, upon the discovery that the application of high pressure compaction to powdered or micronized pharmaceutical preparations can cause physical but non-chemical transformations to an alternative state with substantially slower rates of dissolution and, consequently, increased utility in the preparation of sustained-release formulations. In particular, pharmaceutical preparations subjected to high pressure compaction exhibit dissolution kinetics which

are superior to conventional crystalline or amorphous packed powder preparations for sustained-release administration of active pharmaceutical ingredients.

Without being bound to any particular theory of the invention, it is believed that high pressure compaction causes a physical but non-chemical transformation of state to form pressure-fused particles which, in some embodiments, exhibit hyaline or glassy characteristics but, in other embodiments, retain crystalline or amorphous characteristics. The resultant pressure-fused particles have different dissolution characteristics and, in particular, slower rates of dissolution.

In some embodiments, the high pressure compaction exceeds the apparent glass transition pressure of the pharmaceutical preparation and/or active pharmaceutical ingredient. In some such embodiments, the resultant pressure-fused particles exhibit a hyaline or glassy appearance.

To produce a pressure-fused particle preparation with substantially uniform dissolution characteristics, it is advantageous to ensure an even distribution of force throughout the sample. Therefore, in some embodiments, the sample is rotated during the application of an initial pressure to distribute the material evenly within the press. In addition, in some embodiments, the amount of sample applied to the press is chosen such that the thickness of the material after high pressure compaction is between 25 μm and 400 μm , between 50 μm and 200 μm , or between 100 μm and 150 μm . By evenly distributing the material and reducing the thickness of the sample, a greater degree of uniformity is achieved.

In some embodiments, the amount of pressure required to produce the pressure-fused particles of the invention is between 1 mton/cm² and 100 mton/cm², between 5 mton/cm² and 75 mton/cm², or between 10 mton/cm² and 50 mton/cm². Alternatively, given that 1 giga-Pascal (GPa) is equal to 10.197 mtons/cm², the pressure can be between approximately 0.1 GPa and 10 GPa, between 0.5 GPa and 7.5 GPa, or between 1 GPa and 5 GPa. In some embodiments, this pressure is applied for a period of between 30 sec. and 10 min., between 60 sec. and 5 min., or between 90 sec. and 3 min.

In some embodiments, the amount of pressure is sufficient to produce a compacted sample having a density of between 1 g/cm³ and 40 g/cm³, between 2

g/cm^3 and 20 g/cm^3 , and between 4 g/cm^3 and 10 g/cm^3 . In some embodiments, the amount of pressure is sufficient to produce pressure-fused microparticles having a density of between 1 g/cm^3 and 40 g/cm^3 , between 2 g/cm^3 and 20 g/cm^3 , and between 4 g/cm^3 and 10 g/cm^3 .

5

Particle Dimensions and Shape.

The invention also depends, in part, upon the recognition that, if a larger particle of a pharmaceutical preparation is introduced, there will be a sustained-release effect due to the decreased surface area-to-volume ratio of the larger particles. In addition, if the particle is formulated to be substantially flat or planar, then the kinetics of drug release will more nearly approximate constant or zero-order kinetics. In addition, in some embodiments, the particles of the invention can be used for parenteral administration. For example, in some embodiments, the administration will be by injection (e.g., subcutaneous, intravenous, intramuscular, intraocular), or by introduction to a wound site or during surgery (e.g., lavage or irrigation of a wound or surgical site). In such embodiments, the particles can be sufficiently small to form a suspension and, in certain embodiments, the particles can be sufficiently small for injection through a hypodermic needle. Thus, in some embodiments, the particles have a maximum dimension of between $20 \mu\text{m}$ and $800 \mu\text{m}$, between $40 \mu\text{m}$ and $400 \mu\text{m}$, or between $100 \mu\text{m}$ and $250 \mu\text{m}$.

Thus, in some embodiments, after subjecting a sample to high pressure compaction, the resulting compacted sample can be subjected to sieving to obtain particles of a desired size. For example, the compacted sample can be pressed through a sieve with an exclusion limit of between $20 \mu\text{m}$ and $800 \mu\text{m}$, between $40 \mu\text{m}$ and $400 \mu\text{m}$, or between $100 \mu\text{m}$ and $250 \mu\text{m}$. In addition or alternatively, the compacted samples or sieved particles can be subjected to milling to produce fused particles of smaller size or with different geometries. For example, in some embodiments, pressure-fused particles are milled to produce spheres whereas in other embodiments the pressure-fused particles are milled to produce disks.

In some embodiments of the invention, the pressure-fused particles produced... have at least one linear dimension greater than $20 \mu\text{m}$, greater than $40 \mu\text{m}$, greater

than 100 μm , greater than 250 μm , greater than 400 μm , or greater than 800 μm . In some embodiments, in which the formulations are heterogeneous with respect to particle size, at least 70%, 80%, 90% or 95% of the particles have at least one linear dimension greater than 20 μm , greater than 40 μm , greater than 100 μm , greater than 250 μm , greater than 400 μm , or greater than 800 μm .

Polymeric Coatings.

The pressure-fused particles of the invention can optionally be encapsulated or coated with a polymeric layer or coating according to any method known in the art or subsequently developed. Such polymeric coatings can be useful for improving the sustained-release properties of the particles, or for improving characteristics including, without limitation, administrability, palatability, stability, or shelf-life.

Examples of frequently used and commercially available biocompatible and biodegradable polymers include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ϵ -caprolactone) (PCL), poly(valerolactone) (PVL), poly(ϵ -decalactone) (PDL), poly(1,4-dioxane-2,3-dione), poly(1,3-dioxane-2-one), poly(para-dioxanone) (PDS), poly(hydroxybutyric acid) (PHB), poly(hydroxyvaleric acid) (PHV), and poly(β -malic acid) (PMLA).

More generally, useful polymers include, without limitation, naturally occurring polymers including carbohydrates such as sugar phosphates, alkylcelluloses (*e.g.*, ethylcellulose), and hydroxyalkylcelluloses (*e.g.*, hydroxypropylcellulose); and synthetic polymers or co-polymers including one or more of the following monomers: lactic acid, glycolic acid, β -propiolactone, β -butyrolactone, γ -butyrolactone, pivalolactone, α -hydroxy butyric acid, α -hydroxyethyl butyric acid, α -hydroxy isovaleric acid, α -hydroxy- β -methyl valeric acid, α -hydroxy caproic acid, α -hydroxy isocaproic acid, α -hydroxy heptanic acid, α -hydroxy octanic acid, α -hydroxy decanoic acid, α -hydroxy myristic acid, α -hydroxy stearic acid, α -hydroxy lignoceric acid, β -phenol lactic acid and polyvinyl alcohol. Lactic acid co-polymers offer a degree of flexibility in choosing the life of a polymer matrix, because the half-life can be controlled by varying the amount and type of co-monomer used.

Methods of forming polymeric coatings on particles are well known in the art. For example, standard techniques include solvent evaporation/extraction techniques, in-water drying techniques (*see, e.g.*, U.S. Pat. No. 4,994,281), organic phase separation techniques (*see, e.g.*, U.S. Pat. No. 4,675,19, U.S. Pat. No. 5,639,480),
5 spray-drying techniques (*see, e.g.*, U.S. Pat. No. 5,651,990), triple emulsion techniques (*see, e.g.*, U.S. Pat. No. 4,652,441, U.S. Pat. No. 5,639,480), air suspension techniques, and dip coating techniques.

10 Methods of Administration.

The coated microparticles of the invention are administered parenterally. In some embodiments, the administration is by injection of a suspension of the coated microparticles in a pharmaceutically acceptable carrier, whereas in other embodiments the coated microparticles are administered to an open wound or surgical site.

15 Administration by injection includes, without limitation, subcutaneous, intravenous, intramuscular and intraocular injection. For such routes of administration, the coated microparticles must have a maximum dimension which is less than the inner diameter of the needle used for injection. Although larger needles may be employed to accommodate larger coated microparticles, such larger coated
20 microparticles can have decreased ability to form a suspension. Therefore, in some embodiments, the coated microparticles have a maximum dimension less than the inner diameter of standard needles for parenteral injection. Moreover, the coated microparticles can be chosen to have a maximum size which permits formulation as a suspension in a pharmaceutically acceptable carrier.

25 For parenteral administration to open wounds or surgical sites, the coated microparticles can be administered in a suspension, as described above, or as a solid (*e.g.*, a powder), paste, cream, or ointment. In such embodiments, the coated microparticles can be administered during lavage or irrigation of a wound or surgical site, and the coated microparticles can be substantially larger.

30

Active Pharmaceutical Ingredients.

Active pharmaceutical ingredients which may be formulated according to the invention include any pharmaceutical which may be subjected to the high pressure compaction methods according to the invention without undergoing chemical alteration or degradation which adversely affects its pharmaceutical utility. One of ordinary skill can easily ascertain whether any given active pharmaceutical ingredient is useful in the present invention by preparing a pressure-fused particle and comparing its chemical structure to the active form.

By way of non-limiting examples, potentially useful active pharmaceutical ingredients can be selected from groups including corticosteroids, anti-psychotics, anti-depressants, anti-epileptics, anti-Parkinson agents, anesthetics, narcotics, antibiotics, HIV protease inhibitors, reverse transcriptase inhibitors, HMG CoA reductase inhibitors, calcium channel blockers, β -blockers, angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, taxanes, alkylating agents, immunosuppressive agents, hormones and hormone receptor modulators, as well as other active pharmaceutical ingredients for which sustained-release formulations would be advantageous.

Non-limiting examples of corticosteroids include dexamethasone, triamcinolone, fluocinolone, fluocinolone acetonide, cortisone, prednisolone, fluometholone, clobetasone butyrate, triamcinolone acetonide, betamethasone valerate, diflucortolone valerate, fluticasone valerate, hydrocortisone 17-butyrate, mometasone furoate, methylprednisolone acetate, clobetasol propionate, betamethasone dipropionate, desonide and fluticasone.

Non-limiting examples of anti-psychotics include benzodiazepines such as olanzapine (Zyprexa™), clozapine, loxapine, and quetiapine; benzisoxazole derivatives such as risperidone (Risperdal™) and molindone, and pimozide.

Non-limiting examples of antidepressants include tertiary amine tricyclics such as amitriptyline, doxepin and imipramine; secondary amine tricyclics such as desipramine and nortriptylene; tetracyclics such as mirtazapine; triazolopyridines such as trazadole; aminoketones such as bupropion; phenethylamines such as venlafaxine; phenylpiperazines such as nefazadone; and selective serotonin reuptake

inhibitors (SSRIs) such as citalopram, fluoxetine, fluvoxamine, paroxetine, and
sertaline.

Non-limiting examples of anti-epileptics include hydantoins such as dilantin;
barbiturates such as phenobarbital; deoxybarbiturates such as primidone;
5 iminostilbenes such as cabamazepine; succinimides such as ethosuximide;
benzodiazepines such as clonazepam; as well as valproic acid, gabapentin,
levetiracetam, tiagabine, topiramate and zonisamide.

Non-limiting examples of anti-Parkinson agents include levodopa preparations
such as levodopa benserazide and levodopa/carbidopa; ergot dopamine agonists such
10 as bromocriptine, cabergoline, and pergolide; non-ergot dopamine agonists such
pramipexole, ropinerole, and spomorphine; catechol-O-methyltransferase inhibitors
such as entacapone and tolcapone; monoamine oxidase B inhibitors such as selegiline;
NMDA antagonists such as amantadine; and anticholinergics such as benzhexol,
benztropine, biperiden, orphenedrine, and procyclidine.

15 Non-limiting examples of anesthetics include procaine (Novocain™),
bupivacaine (Marcaine™), lidocaine (Xylocaine™), etidocaine, ropivacaine,
chloroprocaine, tetracaine and mepivacaine.

Non-limiting examples of narcotics include morphine, hydromorphone,
meperidine, fentanyl, propoxyphene, levorphanol, codeine, hydrocodone,
20 oxymorphone, levomethadyl acetate, oxycodone and methadone.

Non-limiting examples of antibiotics include tetracycline antibiotics, such as
tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline,
doxycycline, and minocycline; penicillin antibiotics such as penicillin, chlorpenicillin,
oxypenicillin, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, ampicillin,
25 amoxicillin, bacampicillin, carbenicillin, carbenicillin indanyl, ticarcillin, mezlocillin
and piperacillin; macrolide antibiotics such as erythromycin, clarithromycin and
azithromycin; fluoroquinolone antibiotics such as norfloxacin, ciprofloxacin,
ofloxacin, sparfloxacin, lomefloxacin, fleroxacin, perfloxacin, levofloxacin,
trovafloxacin, gatifloxacin, moxifloxacin and cloxacillin; cephalosporin antibiotics
30 such as cephalothin, cefazolin, cephalixin, cefadroxil, cefamanadole, cefoxitin,
cefaclor, cefuroxime, cefuroxime axetil, loracarbef, cefonicid, cefatetan, ceforanide,

cefotaxime, cefpodoxime proxetil, ceftriaxone, cefoperazone, ceftazidime and cefepime; aminoglycoside antibiotics include gentamicin, tobramycin, amikacin, netilmicin, neomycin, kanamycin, streptomycin, dactinomycin, daunorubicin, bleomycin, plicamycin, and mitomycin; as well as isoniazid (INH), rifampin, 5 rifapentine, pyrazinamide, ethambutol, ethionamide, careomycin and cycloserine.

Non-limiting examples of HIV protease inhibitors include ritonavir, indinavir, nelfinavir, saquinavir, amprenavir and lopinavir.

Non-limiting examples of nucleoside reverse transcriptase inhibitors include the nucleoside-based reverse transcriptase inhibitors zidovudine, didanosine, 10 stavudine, zalcitabine, lamuvudine, and abacavir, and the non-nucleoside-based reverse transcriptase inhibitors include delavirdine, efavirenz and nevirapine.

Non-limiting examples of HMG Co-A reductase inhibitors include simvastatin (Zocor™), lovastatin (Mevacor™), atorvastatin (Lipitor™), pravastatin sodium, fluvastatin and cerivastatin

15 Non-limiting examples of calcium channel blockers include dihydropyridines, such as nifedipine; phenyl alkyl amines, such as verapamil; and benzothiazepines, such as diltiazem; as well as amrinone, amlodipine, bencyclane, felodipine, fendiline, flunarizine, isradipine, nicardipine, nimodipine, perhexilene, gallopamil, tiapamil, phenytoin, barbiturates, dynorphin, omega-conotoxin, and omega-agatoxin.

20 Non-limiting examples of β blockers include propranolol, atenolol, acebutolol, alprenolol, befunolol, betaxolol, bunitrolol, carteolol, celiprolol, hedroxalol, indenolol, labetalol, levobunolol, mepindolol, methypranol, metindol, metoprolol, metrizoranolol, oxprenolol, pindolol, practolol, sotalolnadolol, tiprenolol, tomalolol, timolol, bupranolol, penbutolol and trimepranol.

25 Non-limiting examples of angiotensin II receptor antagonists include saralasin.

Non-limiting examples of ACE inhibitors captopril, zofenopril, enalapril, lisinopril, quinapril, ramipril, perindopril, cilazapril, benazapril, fosinopril and trandolopril.

Non-limiting examples of taxanes include paclitaxel and docetaxel.

30 Non-limiting examples of alkylating agents include the nitrogen mustards, alkyl sulfonate, nitrosurea, ethylenimine and methylmelamine, triazene classes,

cyclophosphamide, ifosamide, thiotepa, melphalan, busulfan, carmustine, clorambucil, hexamethylmelamine and streptozocin.

Non-limiting examples of immunosuppressive agents that suppress the immune system includes the corticosteroids, the purine antagonists such as
5 azathioprine, cyclosporine, tacrolimus, sirolimus and mycophenolate mofetil.

Non-limiting examples of hormones and hormone receptor modulators include insulin, pituitary growth hormone, adrenocorticotrophic hormone, testosterone, progesterone, estrogen, levonorgestrel (Norplant™), tamoxifen, raloxifen and fulvestrant.

10 Non-limiting examples of other active pharmaceutical ingredients potentially useful in the invention include vinca alkaloids such as vincristine and vinblastine; platinum coordination complexes such as cisplatin and carboplatin; isoflavones such as genistein, formononetin, daidzein and equol; epidophylotoxins such as etoposide and teniposide; camptothecins such as topotecan, and iritecan; folic acid analogues
15 such as methotrexate; pyrimidine analogues such as 5-fluorouracil, floxuridine, and cytosine arabinoside; and purine analogues such as 6-mercaptopurine, 6-thioguanine, and 2-deoxycoformycin; as well as the anti-alcoholism medication disulfiram (Antabuse™).

20 The following examples illustrate some specific modes of practicing the present invention, but are not intended to limit the scope of the claimed invention. Alternative materials and methods may be utilized to obtain similar results.

EXAMPLES

25

Formation of Pressure-Fused Particles.

Pressure-fused particles were prepared from the active pharmaceutical ingredient olanzapine, an atypical antipsychotic drug, obtained in micronized form (90% of particles <5 µm in diameter) from a commercial supplier (Dr. Reddy Labs,
30 Upper Saddle River, NJ). The lower punch of a hydraulic press used for producing IR pellets was placed into a die with an 8 mm diameter, and approximately 30 mg of

olanzapine was loaded into the die. The upper punch was placed into the die, and moderate pressure was applied by hand to pack and evenly distribute the active pharmaceutical ingredient in the die. The die assembly was seated in the press and force was increased to 25-30 mtons and maintained for a minimum of 30 seconds, and typically 90 seconds. Given that the die had a diameter of 8 mm, the area of the die was approximately 0.50 cm^2 and, therefore, the pressure was 50-60 mtons/ cm^2 . Alternatively, given that 1 GPa is equal to 10.197 mtons/ cm^2 , the pressure was approximately 5-6 GPa.

Given an initial sample of 30 mg compacted into a sample of 8 mm diameter and 150 μm thickness, the density of the compacted sample was approximately 4 g/cm^3 .

The high pressure compaction produced a "fused" or "glassy" wafer of olanzapine that was removed from the press. The compacted sample was then forced through a 60 mesh sieve grating with apertures of approximately 250 μm to produce roughly cuboidal particles.

Formation of PVA Polymeric Coating.

Polyvinyl alcohol (PVA) was obtained with a mol. wt. range of 124,000-186,000. Excess PVA was heated in water at 65°C . After cooling, the PVA solution was decanted and mixed with core particles prepared as described above. The core particles were swirled in a beaker of the PVA solution for several seconds, and vacuum-filtered onto #42 filter paper (Whatman, Inc., Clifton, NJ) in a 9 cm diameter Buchner funnel. The filter paper with retained coated core particles was transferred to a watch glass and dried at 155°C or 165°C for 10 minutes. This process was repeated 4-5 times.

Dissolution Testing.

The dissolution of micronized olanzapine (90% of particles $<5 \mu\text{m}$ in diameter) from a commercial supplier (Dr. Reddy Labs, Upper Saddle River, NJ) was compared with the dissolution of coated microparticles of olanzapine prepared as described above.

Powder dissolution testing was carried out in distilled water at 25°C. A 2-3 mg sample of the powder in 25 ml of water was 50% dissolved at approximately 1 minute, and was completely dissolved in 2.5 minutes.

Coated microparticle dissolution testing was also carried out in distilled water at 25°C. A 2-3 mg sample was placed in 25 ml of water. The microparticles were completely covered by the solution. Every 24 h for 5 days, 5 ml of the supernatant solution was carefully removed and replaced with fresh media, avoiding mixing of the buffer, to simulate physiological "sink" conditions. Figure 1 represents the data regarding the release of the active pharmaceutical ingredient from the coated microparticles over time. As shown in the figure, the rate of release was substantially constant or pseudo-zero-order over several days. The release rate from the PVA-coated microparticles dried at the lower temperature was greater, indicating that drying temperature can be used to vary permeability and release rate.

15 Active Pharmaceutical Ingredient Stability.

To determine whether the formation of the core particles or polymeric coatings altered or degraded the active pharmaceutical ingredient, high performance liquid chromatography (HPLC) was employed. An HP 1050 HPLC System chromatograph (Agilent Technologies, Palo Alto, CA) with variable wavelength detector was used with a silica HPLC column (Grace Vydac, inc., Columbia, MD, Product #101TP54) with normal phase (unbonded), 300Å pore size, 5 µm particle size, 4.6 mm x 250 mm. The injection volume was 20 µl, with a flow rate of 1.0 ml/min at 25°C (ambient). The pump was operated in isocratic mode, the post time was 3.0 minutes, and absorbance at 254 nm was measured. The mobile phase was 50:50 chloroform:isooctane.

The samples were taken from the dissolution tests described above. HPLC analysis performed confirmed the purity of the olanzapine from the coated microparticles of the invention and the absence of breakdown products.

In Vivo Studies.

The active pharmaceutical ingredients nifedipine (a calcium channel blocker), carbamazepine (an anti-epileptic), cyclosporine (an immunosuppressive agent), and ciprofloxacin (an antibiotic) were prepared as compacted samples according to the methods of the invention. In each case, a sample of 30-40 mg of the active pharmaceutical ingredient was subjected to very high pressure compaction of approximately 5-6 GPa to produce a compacted sample measuring approximately 8 mm in diameter and approximately 125-200 μm in thickness. The resulting compacted sample was broken into fragments to weigh-out an appropriate amount for administration to animals as described below.

Given initial samples of 30-40 mg compacted into samples of 8 mm diameter and 150 μm thickness, the densities of the compacted samples were approximately 3.9-5.3 g/cm^3 .

For each active pharmaceutical ingredient, 3-5 male Sprague-Dawley rats were cannulated through the jugular vein to allow venous access. After general anesthesia with a combination of ketamine (60 mg/kg) and medetomidine (0.3 mg/kg) administered intraperitoneally, the backs of the rats were shaved and an incision approximately 6 mm in length was made in the skin. The subcutaneous tissues were spread using blunt scissors and 6 mg/kg of the compacted sample was placed into the subcutaneous tissues approximately 5 mm from the incision site. The incision was closed with staples and topical antibiotic applied.

Venous samples were taken through the cannula periodically for approximately two weeks to determine plasma levels of the active pharmaceutical ingredients. The assays had sensitivities of approximately 1 ng/ml.

Histological examination of the implantation sites was carried out in all animals. Animals appeared to remain healthy and to gain weight normally. By post-mortem histological examination of the implantation sites, there was no evidence of local toxicity, tissue reaction or infection.

The results for nifedipine are shown in Figure 2, for carbamazepine in Figure 3, for cyclosporine in Figure 4, and for ciprofloxacin in Figure 5. In general, these

results show a more constant rate of release than standard pharmaceutical preparations of micronized particles.

Equivalents.

- 5 While this invention has been particularly shown and described with references to specific embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. Those skilled in the art will recognize, or be able to ascertain using no more than routine
- 10 experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the appended claims.